Influence of Drug Release Properties of Conventional Solid Dosage Forms on the Systemic Exposure of Highly Soluble Drugs

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ABSTRACT This study was designed to theoretically investigate the influence of drug release properties, characterized by the disintegration of a solid dosage form and dissolution of drug particles, on the systemic exposure of highly soluble drugs in immediate release products. An absorption model was developed by considering disintegration of a solid dosage form, dissolution of drug particles, gastrointestinal transit flow, and intestinal absorption processes. The absorption model was linked to a conventional pharmacokinetic model to evaluate the effect of disintegration and dissolution on the peak exposure (C_{max}) and total exposure of area under the curve (AUC). Numerical methods were used to solve the model equations. The simulations show that the effect of disintegration of a dosage form and dissolution of drug particles depend on the permeability of a drug, with a low-permeability drug having a greater effect. To provide similar exposure to an oral solution formulation, a solid dosage form containing a low-permeability drug would need to dissolve more rapidly than a solid dosage form containing a high-permeability drug. It was shown theoretically for poorly permeable drugs that the disintegration rate constant has to be greater than 9 hour $^{-1}$ (equivalent to approximately 90% in 30 minutes) to make both AUC and C_{max} ratios higher than .9, ensuring the confidence interval of .80 to 1.25. The rapid in vitro release requirement of at least 85% dissolved in 30 minutes is sufficient for highly soluble and highly permeable drugs. However, for highly soluble and poorly permeable drugs, the appropriate in vitro release requirement seems to be 90% dissolved in 30 minutes.

KEYWORDS: Small intestinal transit, dissolution, disintegration, absorption modeling, bioequivalence.

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INTRODUCTION

The US Food and Drug Administration issued a guidance on waiver of in vivo bioavailability and bioequivalence studies for immediate-release, solid, oral dosage forms in August 2000[1] . The guidance is based on the proposed Biopharmaceutics Classification System (BCS)[2] and recommends that sponsors apply for biowaivers for *highly soluble* and *highly permeable* drug substances (BCS Class I) in immediate-release, solid, oral dosage forms that exhibit *rapid in vitro release* . It has been suggested recently that the waiver of in vivo bioequivalence studies should be extended to highly soluble and poorly permeable drugs (BCS Class III)[3] . It is unknown, however, what kind of in vitro drug release requirements should be set to ensure that the drug release has no significant effect on in vivo bioavailability. Despite recent advances in absorption modeling and simulation[4-8], the relationship between in vivo absorption processes and in vitro drug product release has not been well defined; current absorption models account for the dissolution of drug substance, but not for drug product release. Furthermore, drug product release modeling is based mainly on empirical or semi-empirical models[9]. Potential drug excipient interactions certainly add to the complexity of drug release modeling[10].

This report aims to establish relationships between absorption processes and drug release properties of a formulation. It investigates how drug substance dissolution and drug product disintegration affect the peak exposure (C_{max}) and total exposure of the area under the curve (AUC) of highly soluble drugs in immediate-release dosage forms using a solution dosage form as a reference. To this end, an in vitro drug release model of a solid dosage form was proposed and an in vivo absorption model was developed. Simulations were conducted to establish appropriate in vitro drug release requirements to ensure in vivo drug release would not cause bioinequivalence for highly soluble and poorly permeable drugs.

MATERIALS AND METHODS

THEORETICAL

In Vitro Drug Release Model

As shown in **Figure 1** , the drug release property of a solid dosage form may be characterized by 2 subprocesses: the liberation of drug particles from a dosage form and the dissolution of drug from the liberated drug particles. It is assumed that the dissolution of drug from the surface of the intact dosage form is negligible. Mathematically, these 2 subprocesses may be expressed as

$$\frac{dM_f}{dt} = -K_f M_f \quad (1)$$

$$\frac{dM_d}{dt} = K_f M_f - K_d (M_d / M_0)^{2/3} (C_s - C_l) \quad (2)$$

$$\frac{dM_l}{dt} = K_d (M_d / M_0)^{2/3} (C_s - C_l) \quad (3)$$

where M_f , M_d , and M_l are the amount of drug remaining in the formulation, in the particles, and in the liquid; K_f and K_d are the drug product disintegration and drug substance dissolution rate constants; V is the volume of dissolution medium; M_0 is the dose; and C_s and C_l are the solubility and drug concentration in liquid ($M_l = C_l \times V$).

Equation 1 assumes that the drug particle liberation from the dosage form is a first-order process, as suggested in the literature[11] . This is a simplification of a complex process. The factors influencing the liberation of drug particles from dosage forms include formulation and processing factors, such as diluent, disintegrant, binder and granulating agent, lubricant, method of granulation, and compression force. For convenience, we use the term "disintegration" to describe the whole process and we assume that the formulation and process variables are reflected in the disintegration rate constant, K_f. Clearly, the disintegration described here is not equivalent to the disintegration discussed in the in vitro drug release testing.

Equations 2 and 3 are the same as the model proposed in the literature[5] . The dissolution rate constant Kd in equations 2 and 3 can be calculated by

$$K_d = \frac{3DM_0}{\rho h r_0} \quad (4)$$

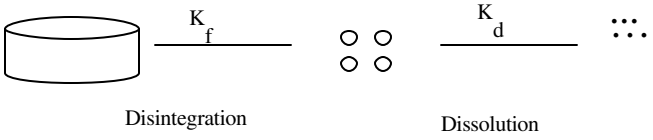

Figure 1. A schematic of disintegration and dissolution processes, where the disintegration is considered as a first-order process and the dissolution from drug particles is proportional to the concentration difference between the particle surface and bulk solution. The disintegration considers the effect of formulations and manufacturing process variables, whereas the dissolution from drug particles mainly considers the effect of solubility and particle size.

where D is the diffusion coefficient, M_0 is the dose, ρ is the density of drug, h is the aqueous diffusion layer thickness, and r_0 is the initial radius of particles. The model takes no account of particle size distribution, the change of aqueous boundary thickness, and the changes of the surface area per unit weight. However, the dissolution model was able to predict the dissolution of digoxin, griseofulvin, and panadiplon reasonably well[5] .

In Vivo Absorption Model

The in vivo absorption model used in this study was developed based on our previously published model[5], which not only considers intestinal absorption and dissolution from drug particles, but also drug liberation from dosage forms (ie, disintegration). It is assumed that the model equations of drug release in vivo are similar to those in vitro except that the drug release volume may be different. The assumptions with the model include the following:

1. Absorption from the stomach and colon is insignificant compared with that from the small intestine. The transport across the small intestinal membrane is passive, and the amount of drug transported is equal to its uptake.

2. Liquid and solid drug moving through the small intestine can be viewed as a moving process flowing through a series of segments, each described by a single compartment with linear transfer kinetics from one compartment to the next, and all compartments having different volumes and flow rates but the same residence times[8] .

3. Drug product or formulation excipients have no significant impact on gastrointestinal motility and intestinal permeability; disintegration, dissolution, and absorption rate constants are site-independent.

Therefore, incorporating the disintegration process into our previous in vivo model equations[4,5] results in the following model equations:

$$\frac{dM_{nf}}{dt} = K_t M_{(n-1)f} - K_t M_{nf} - K_f M_{nf} \quad (5)$$

$$\frac{dM_{nd}}{dt} = K_t M_{(n-1)d} - K_t M_{nd} + K_f M_{nf} - \frac{K_d M_{nd}}{M_0^{2/3}(\sum M_{nd})^{1/3}}(C_s - C_{nl}) \quad (6)$$

$$\frac{dM_{nl}}{dt} = K_t M_{(n-1)l} - K_t M_{nl} + \frac{K_d M_{nd}}{M_0^{2/3}(\sum M_{nd})^{1/3}}(C_s - C_{nl}) - K_a M_{nl} \quad (7)$$

where n = 1, 2, 3, ..., 7, K_t is the transit rate constant[12] , and K_a is the absorption rate constant. The overall rate of drug absorption can be calculated by

$$\frac{dM_a}{dt} = K_a \sum_{n=1}^{7} M_{nl} \quad (8)$$

where M_a is the amount of drug absorbed at time t.

In Vivo Pharmacokinetic Model

The rate of drug absorption (equation 8) can be linked to any conventional pharmacokinetic model. Assuming a 1-compartment model with first-order elimination, we have

$$\frac{dC}{dt} = \frac{1}{V_1}\frac{dM_a}{dt} - k_e C \quad (9)$$

where C is the plasma concentration, V_1 is the volume of distribution, and ke is the first-order elimination constant. From equation 9, the AUC and C_{max} can then be estimated.

METHODS

Solution of Model Equations

Model equations 1-9 are a typical initial value problem of an ordinary differential equation system. This system was numerically solved by the ADAPT II pharmacokinetic and pharmacodynamic modeling package to estimate the peak exposure and total exposure[13]. A subroutine was written to accommodate the model equations.

Model Parameters

Table 1 shows the values of model parameters used in the simulation. The dose of the model drug is assumed to be 100 mg. Based on the dose, the BCS boundary value of solubility that determines the solubility membership of a compound was calculated to be .4 mg/mL. The fraction of dose absorbed of 90% corresponds to an absorption rate constant of .82 h^{-1} based on prediction model equation 3. The elimination rate was assumed to be .23 h^{-1} , which corresponds to a half-life of 3 hours. The volume of distribution was assumed to be 100 L. The volumes of the gastrointestinal tract compartments were taken from the literature[14] .

In vivo absorption was simulated by considering high (4.1 h^{-1}) and low (0.082 h^{-1}) absorption rate constants, which correspond to high and low permeabilities of 1.0 x 10^{-3} and 2.0 x 10^{-5} cm/s based on $K_a = 2P_{eff}/R$, where R is the small intestinal radius 1.75 cm. The permeability of 2.0 x 10^{-5} cm/s corresponds to the fraction of dose absorbed of .23, implying the maximum bioavailability of 23%.

In Vitro Drug Release and In Vivo Absorption

Simulations of in vitro drug release were conducted for highly soluble drugs. The simulated in vitro drug release was then compared with the in vivo absorption to estimate the in vitro drug release rate necessary to provide similar exposure to a solution dosage form. The in vitro drug release was characterized by the percent dissolved at 30 minutes. In vivo absorption was described by the peak and total exposure ratios of a solid dosage form relative to an oral solution to identify where a solid dosage form would perform like a solution in vivo.

The effect of gastric emptying was not considered, and the drug product was assumed to be administered directly into the duodenum. The stomach acts like a regulator, and gastric emptying of dosage forms varies significantly[15] . In general, the longer the gastric emptying time, the less the effect of disintegration and dissolution on absorption, provided that the test and reference formulations are emptied at the same rate. Thus, ignoring the effect of gastric emptying represents the worst-case scenario and provides a conservative estimate of in vitro release rate.

RESULTS

In Vitro Drug Release

Figure 2 (A) shows a drug release profile of a solid dosage form containing a drug with the solubility of .4 mg/mL in the dissolution volume of 900 mL, commonly used in USP dissolution apparatus I and II. **Figure 2** (A) also shows the amount of drug particles in the dissolution medium and the amount of solid drug remaining in the tablet. For a particular product, we can vary the disintegration and dissolution constants to achieve the desired dissolution profiles. Therefore, the drug release model covers both drug substance and drug product attributes.

Figure 2 (B) shows the effect of disintegration rate constant on the in vitro drug release profile, where the dissolution rate constant was kept constant (K_d = 1600 mL/h). Because each product uses the same drug substance, we can reasonably assume that each has a similar dissolution rate constant K_d , provided that the manufacturing process will not alter the particle size of drug substance and that there is no drug excipient interaction. This simulation is for products where the particle size specification is the same for all drug substances. Consequently, the difference in dissolution profiles is mainly caused by the differences in dosage forms, reflected in the disintegration rate constant.

Figure 2 (C) shows the percent of dose dissolved at 30 minutes as a function of disintegration and dissolution constants, K_f and K_d , respectively. **Figure 2** (C) gives the levels of K_f and K_d needed to ensure rapid drug release in vitro (at least 85% in 30 minutes). It remains to be shown how dosage forms affect in vivo pharmacokinetics. In other words, how do the observed differences of in vitro drug release translate into in vivo?

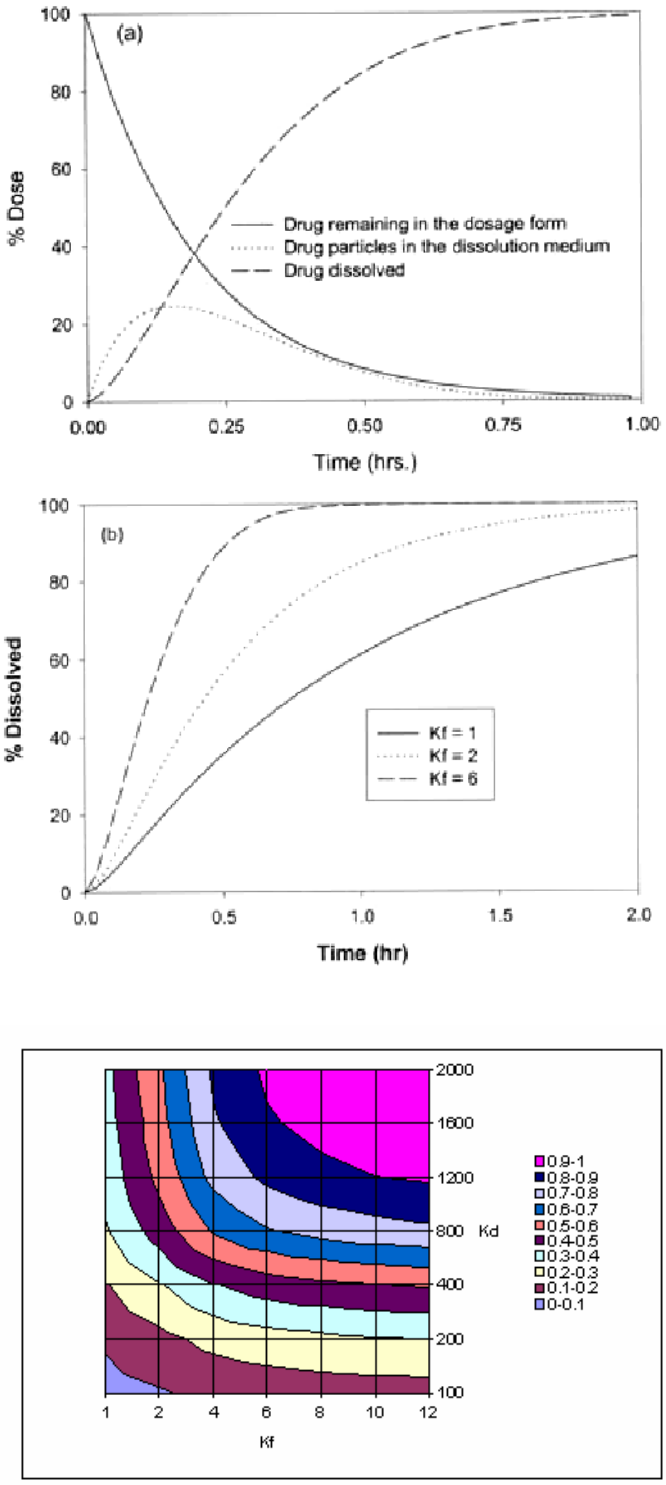

Figure 2. (A) The percent drug in the dosage form, in particles, and dissolved as a function of time, where K_f = 5 h^{-1} , K_d = 1600 mL/h. and (B) Effect of disintegration on drug release, where K_d = 1600 mL/h. The disintegration time can be calculated by 1/K_f . Thus, the K_f values of 1, 2, and 6 h^{-1} correspond to the disintegration (residence) times of 1, .5, and .17 hours and and (C) In vitro drug release, characterized by percent dissolved at 30 minutes, as a function of disintegration and dissolution constants (K_f and K_d). The figure shows the percent dissolved at 30 minutes given the values of the disintegration and dissolution rate constants.

In Vivo Absorption

For highly soluble and highly permeable drugs, oral drug absorption is complete before it reaches the end of the small intestine. Thus, the dosage form or disintegration may not reduce the AUC, although it may alter the onset of absorption and affect the C_{max} . For the purpose of simulation, **Figures 3** (A) and (B) show the effect of K_f and K_d on AUC and C_{max} ratios using an oral solution as a reference (that is, AUC [tablet]/AUC[solution] and C_{max} [tablet]/C_{max} [solution]) for highly soluble and highly permeable compounds. **Figure 3** (A) shows that disintegration has limited effect on AUC. An example of such a compound is acetaminophen-only a small portion of small intestine is required to reach complete absorption. Even with the disintegration rate constant of 1 $hour^{-1}$, which corresponds to a disintegration time of 1 hour (h), there are still 2.2 hours of transit time left for absorption based on the mean small intestinal transit time of 3.32 hours (4). Consequently, the simulation outcome shown in **Figure 3** (A) is as expected. Nevertheless, disintegration does affect the C_{max} , as shown in **Figure 3** (B). This implies that prolonging disintegration will reduce the C_{max} while keeping the AUC similar for highly soluble and highly permeable drugs. **Figures 3** (A) and (B) show that the disintegration can be the absorption rate-limiting step; however, the current rapid drug release criterion (>85% at 30 minutes) is more than sufficient to prevent this from occurring. For example, for a drug with solubility .4 mg/mL, Kd was calculated to be 1200 mL/h from equation 4, based on the dose of 100 mg, diffusion coefficient of 5 ' 10^{-6} cm^2 /sec, density of 1200 mg/mL, aqueous diffusion layer of 30 mm, and particle size of 25 mm. Thus, from **Figures 3** (A) and (B), K_f has to be greater than 2.5 to make both the AUC and C_{max} ratios higher than .9, ensuring the confidence interval of .8 to 1.25. Based on the K_d and K_f values, **Figure 2** (C) gives the percent dissolved at 30 minutes around 60%, well below the criterion of 85%.

Figures 4 (A) and (B) show the effect of disintegration and dissolution rate constants on the AUC and C_{max} ratios for highly soluble and poorly permeable drugs. Example drugs are acyclovir and enalaprilate (in terms of permeability). **Figures 4** (A) and (B) show that AUC and C_{max} are more sensitive to the disintegration and dissolution rate constants for poorly permeable drugs. In contrast to the highly soluble

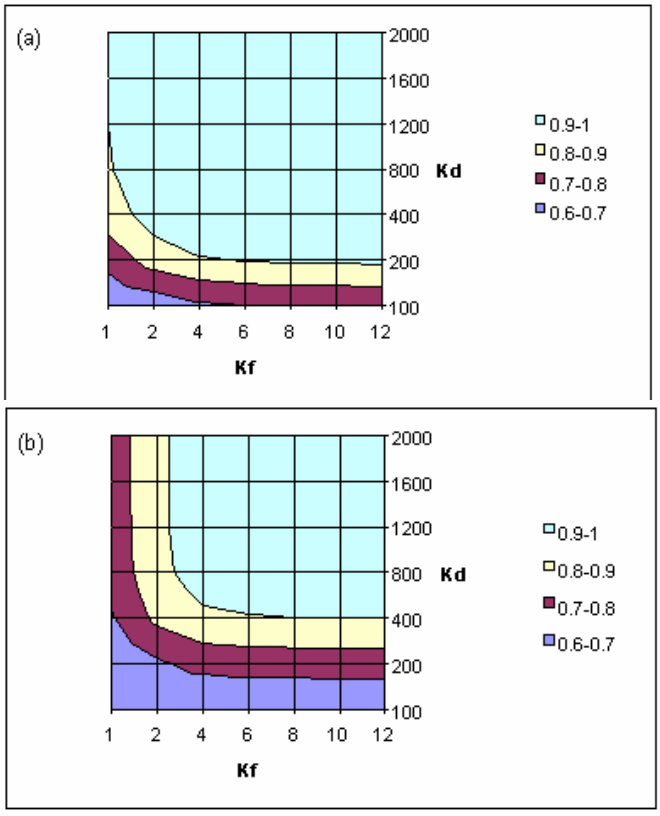

Figure 3.(A) The total exposure of area under the curve (AUC) and (B) peak exposure (C_{max}) ratios of solid dosage forms in reference to an oral solution as a function of the disintegration and dissolution rate constants for *highly soluble* (.4 mg/mL) and *highly permeable* (1.0 x 10^{-3} cm/sec) compounds. The figure shows the requirements of K_f and K_d values to make a solid dosage form to be bioequivalent to an oral solution formulation. When compared with Figure 2(C), the requirements of in vitro dissolution can be determined based on the assumption of the same K_f and K_d in vivo and in vitro.

soluble and highly permeable drugs (**Figure 3**), where the C_{max} is more sensitive than AUC for highly soluble and poorly permeable drugs, AUC is more sensitive than C_{max} . Using the same example above but reducing the permeability from 1.0 x 10^{-3} cm/s to 2.0 x 10^{-5} cm/s, the disintegration rate constant has to be greater than 9 h^{-1} to make both AUC and C_{max} ratios higher than .9, ensuring the confidence interval of .8 to 1.25. From **Figure 2** (C), we can see that the percent dissolved at 30 minutes is now around 89%, based on K_d of 1200 mL/h and K_f of 9 h^{-1} . Therefore, compared with highly permeable drugs, higher in vitro drug release requirements are needed. The current rapid drug release criterion (85% dissolved at 30 minutes) is not likely sufficient to ensure bioequivalence in vivo between solid and solution formulations.

Model Assumptions

This model assumes the same absorption rate constant throughout the small intestine, suggesting that the simulation outcome applies only to passively transported drugs. It is further assumed that in vitro and in vivo dissolution have the same disintegration and dissolution rate constants. Because the disintegration may be improved in vivo with the presence of bile acids, the assumption of the same disintegration rate constant in vivo and in vitro may be a conservative estimate.

The model further assumes that there is no significant absorption from the stomach or colon for passively transported drugs. It should be noted that many passively transported drugs could be absorbed from the colon and that the situation actually can be improved if the compound is absorbed from the colon. Therefore, from a regulatory point of view, the assumption is more conservative.

Equation 4 shows that the aqueous diffusion layer thickness is the most likely factor that can make the K_d difference between in vivo and in vitro because this is the only factor that depends on the external environment (ie, hydrodynamics). Recent experimental evidence suggests that the dissolution results in vitro are much lower than expected in vivo[16] ; therefore, the assumption of the same disintegration and dissolution rate constants in vitro and in vivo may also be relatively conservative.

CONCLUSION

A novel absorption model was developed by incorporating gastrointestinal transit flow, intestinal absorption, and drug release properties of solid dosage forms. The results of this simulation suggest that the current rapid drug release criterion (> 85% dissolved in less than 30 minutes in .1 HCl, pH 4.5, and pH 6.8 buffers) may ensure the bioequivalence of solid dosage forms containing highly soluble and highly permeable drugs, but not highly soluble and poorly permeable drugs. The appropriate in vitro release requirements seem to be 90% dissolved in 30 minutes for highly soluble and poorly permeable drugs.

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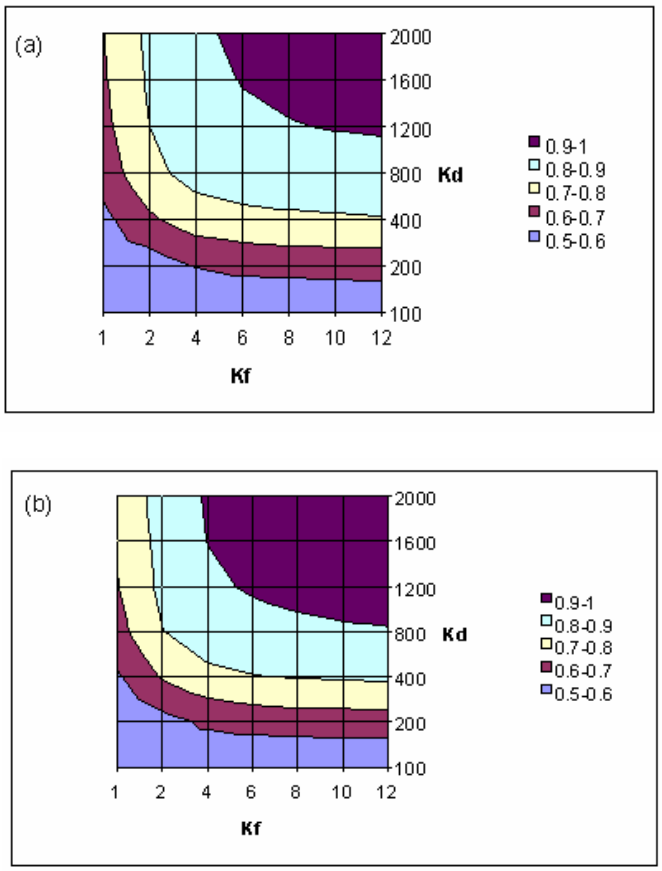

Figure 4(A) The total exposure of area under the curve (AUC) and (B) peak exposure (C_{max}) ratios of solid dosage forms in reference to an oral solution as a function of the disintegration and dissolution rate constants for *highly soluble* (.4 mg/mL) and *poorly permeable* (2.0 x 10^{-5} cm/sec) compounds. The figure shows the requirements of K_f and K_d values to make a solid dosage form to be bioequivalent to an oral solution formulation. When compared with Figure 2(C), the requirements of in vitro dissolution can be determined based on the assumption of the same K_f and K_d in vivo and in vitro.

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